# Loco-regional intervention for hepatocellular carcinoma

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ABSTRACT

Anatomic location/size and number of lesions, inadequate volume of future liver remnant, or poor coexisting premorbid conditions preclude surgery in the majority of patients with hepatocellular carcinoma (HCC). Liver transplantation can cure some patients with poor liver function, but few patients are eligible because of scarcity of donors. Without specific anti-cancer treatment, the prognosis of HCC is poor. Various locoregional therapies are used to treat patients who are not candidates for surgery, and have emerged as tools for palliation, tumor down-staging, and bridging therapy prior to liver transplantation. Currently, local ablative therapy even competes with partial hepatectomy and liver transplantation as a primary treatment for small HCC. HCC is well suited to treatment with loco-regional therapy because it has a tendency to stay within the liver, with distant metastasis generally occurring late in the course of disease. This suggests that an effective local-regional therapy can have a great impact on HCC patients who are not candidates for surgical treatment. Loco-regional therapy can further be justified because patients with HCC usually die of liver failure consequent to intrahepatic growth resulting in liver tissue destruction, rather than extrahepatic metastases.

## Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third leading cause of cancer-related death worldwide. About 80% of all cases occur in Asia.[1–3] The goal of HCC management is "cancer control" with reduction in its incidence and mortality rates and improvement in quality of life of HCC patients. Overall, about 80% of HCC can be attributed to chronic hepatitis B and/or C infection. Prevention of infection with hepatitis B and C virus is the key to reduce the incidence of HCC. However, liver resection and liver transplantation remain the options that give the best chance of a cure in patients who have developed HCC. In the past 3 decades, operative mortality and long-term surgical outcomes of liver resection and liver transplantation for HCC have significantly improved. However, only 10–20% of HCC is resectable. Anatomic location/size and number of lesions, inadequate liver volume of future remnant, or poor coexisting premorbid conditions preclude surgery in the majority of patients with HCC. Liver transplantation can cure some patients with poor liver function, but few are eligible because of scarcity of donors. Without specific anti-cancer treatment, the prognosis of HCC is poor. Various loco-regional therapies are used to treat patients who are not candidates for surgery, and have emerged as tools for palliation, tumor down-staging, and bridging therapy prior to liver transplantation. Currently, local ablative therapy even competes with partial hepatectomy and liver transplantation as a primary treatment for small HCC. HCC is well suited to treatment with loco-regional therapy because it has a tendency to stay within the liver, with distant metastasis generally occurring late in the course of disease. This suggests that an effective loco-regional therapy can have a great impact on HCC patients who are not candidates for surgical treatment. Loco-regional therapy can further be justified because patients with HCC usually die of liver failure consequent to intrahepatic growth resulting in liver tissue destruction, rather than extrahepatic metastases.[2–6]

This article aimed at reviewing the recent advances in loco-regional therapies for HCC.

## Local ablative therapy (LAT)

LAT is being increasingly used to treat HCC. It is currently considered as the best therapeutic modality for patients with small HCCs confined to the liver, especially for tumors which are unresectable due to poor general condition, or compromised liver function. Several techniques of LAT have been developed, including chemical ablation using acetic acid or ethanol, and thermal ablation using radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation and laser ablation. RFA is now most commonly used. MWA is increasingly used to treat large HCC and lesions near to large vessels to overcome the heat-sink effects.

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RFA induces thermal injury through delivery of electromagnetic energy. The application of rapidly alternating radiofrequency current results in marked ionic agitation and frictional heat generation around the electrode, leading to coagulative necrosis of tissues. The degree of thermal injury depends both on the temperature achieved and the duration of heating. Irreversible cellular damage occurs if the tissue is heated at 50–55 °C for 4–6 min. The ablative system includes a RF generator, an electrode needle and a large dispersive electrode (the ground pads), which together completes a closed-loop circuit through the patient. When compared with ethanol injection, RFA achieves more effective local control of disease with fewer treatment sessions, and is therefore superior. The amount of necrosis induced by RFA is also more predictable. RFA is a safe procedure with very low rates of death and major complications. The reported mortality and major complication rates ranged from 0% to 1.4%, and, 2.4%–12.7%, respectively. Most complications are transient and self-limiting. Complications resulting from RFA can be divided into two broad categories: complications secondary to RFA electrode placement and those secondary to thermal injury or tissue necrosis. The former category includes infection, bleeding, tumor seeding, and pneumothorax. The latter category includes post-ablation syndrome, thermal damage to adjacent organs and grounding pad burns. Some complications occur more frequently with percutaneous RFA than surgical RFA (e.g. gastrointestinal perforation, cholecystitis, pleural effusions, skin burns, tumor seeding). RFA for HCC can be accomplished using an open, laparoscopic, or percutaneous approach. The laparoscopic and open approaches increase the chance to detect undiagnosed intrahepatic and extrahepatic tumors because these approaches allow complete abdominal exploration and intraoperative ultrasound (IOUS) assessment. The additional advantages of open and laparoscopic approaches are accurate placement of electrodes, possible treatment of tumors which are inaccessible by the percutaneous approach and treatment of tumors which are in close proximity to, or have invaded, adjacent organs. The advantages of the open approach are lost but the advantages of minimal invasiveness are gained with change from open, to laparoscopic and then to percutaneous approach.[2,4]

MWA, also a form of LAT, involves the use of microwave energy, which causes molecular vibration of dipoles, especially water molecules in tissues, to produce dielectric heat and thermal coagulation around the electrode. No grounding pads are needed. MWA has the advantages of a high thermal efficiency and is a relatively fast procedure. The time required to ablate is short and the shape of necrosis is elliptical. There is no heat-sink effect and it can be used to ablate tumors adjacent to major vessels. However, it can coagulate blood vessels, especially small vessels. These factors yield a larger ablation volume, and result in good local control and few complications. Moreover, as MWA does not depend on passage of electricity through tissues as RFA does, multiple applicators can be applied simultaneously to create a large ablation zone and shorten the procedure time. A recent meta-analysis which included one randomized controlled trial (RCT) and 6 retrospective studies with 774 patients showed similar efficacies between percutaneous RFA and MWA, but with an apparent superiority of MWA in large tumors.[7,8]

LAT is currently considered as an alternative to liver resection for patients with an early-stage HCC. Current studies using RFA to treat HCC have produced survival outcomes to such a point that RFA is beginning to challenge liver resection as a first line treatment for HCC. In the cohort study reported by Livraghi et al., 218 patients with a solitary and resectable HCC < or = 2 cm who underwent RFA, the perioperative mortality, major complication, and 5-year survival rates were 0%, 1.8%, and 68.5%, respectively.[9] In the cohort study reported by Shiina et al., of 2982 RFA treatments on 1170 HCC patients with a mean tumor size of 2.54 cm, computed tomography imagings showed complete tumor ablation in 2964 (99.4%) of all the treatments. After a median follow-up of 38.2 months, the 5- and 10-year survival rates were 60.2% and 27.3%, respectively. There were 67 complications (2.2%) and 1 death (0.03%).[10] However, a number of randomized studies comparing RFA with liver resection showed conflicting results.[11–16] A recent meta-analysis found

the indications for RFA as a primary treatment for patients who are eligible for liver resection with early stage HCC is unclear.[17] Five randomized studies examining 742 patients were included in that study. The meta-analysis showed that RFA and liver resection had similar overall survival rates at 1 year and 3 years, whereas RFA resulted in a significantly decreased overall survival rate compared with liver resection at 5 years. The trial sequential analysis concluded that more trials were needed to control random errors. The incidence of overall recurrence was markedly higher and the hospitalization duration was significantly shorter in the RFA group than the liver resection group. These results were confirmed by the trial sequential analysis. Although the complication rate was less frequent in the RFA group, but the trial sequential analysis showed that additional trials were necessary to confirm this finding.

## Regional therapy

### Transarterial chemoembolization

Regional therapies include transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE), drug eluting bead (DEB) transarterial chemoembolization (DEB-TACE), and transarterial radioembolization (TARE). The liver has a dual blood inflow supply via the portal vein and the hepatic artery. Normally, the portal vein is responsible for supplying most of the blood to the liver (75–83%), with the hepatic artery providing only a supportive role (20–25%). However, this balance is profoundly altered in HCC in which the hepatic artery practically becomes the sole supplier of blood to the tumor (90–100%). It is precisely this anatomic configuration that is being exploited in regional therapy. The hepatic artery is used as a roadway to treat the tumor while the non-tumorous liver is less affected by the treatment.[5]

cTACE, the most widely practiced transarterial therapy, combines transcatheter delivery of chemotherapeutic drugs with lipiodol emulsion, followed by obstruction of the arterial blood supply by a variety of embolic agents to achieve a combined cytotoxic and ischaemic effect. The injection of chemotherapeutic agents into the feeding artery of the tumor aims to expose tumor cells to high concentrations of chemotherapeutic drugs and at the same time reduce systemic side effects of the drugs. Similarly, the non-tumorous liver tissues are only minimally affected by partial or complete occlusion of the hepatic arterial blood supply. To prolong the contact time between tumor cells and the chemotherapeutic drugs, the drugs are emulsified with lipiodol before intra-arterial administration. Lipiodol is a radio-contrast which is selectively retained in HCC for weeks, or even months. The emulsion, at least in vitro, allows a slow release of the drug(s) from the lipiodol microdroplets, lasting hours, if not days. The concentration of chemotherapy within the tumor tissues can be 10–100 times higher after TACE using lipiodol than after systemic chemotherapy. Moreover, embolization of capillaries by these droplets further enhances the exposure time to the active agent(s) by slowing its (their) escape from the tumor. A greater absorption of these chemotherapeutic agent(s) by tumor cells can be achieved because of the ischemic-induced failure of the transmembrane pump in tumor cells by the lipiodol droplets. In addition, particle embolization of the tumor feeding arteries renders the tumor ischemic, and results in subsequent tumor necrosis. The combination of highly concentrated chemotherapy and some degree of ischemia within the tumor is likely to be synergistic in achieving tumor necrosis. Also, embolization reduces the arterial inflow to tumors to allow the chemotherapeutic agent(s) to remain in contact with tumor cells for a prolonged period of time. Moreover, when embolization follows the injection of an anticancer drug into the hepatic artery, blockage of the tumoral circulation limits washout of drug(s) from the tumor, thus increasing the anti-tumor effect and reducing the systemic side effects of the chemotherapy. However, cTACE is a heterogeneous and not a standardized technique. A variety of chemotherapeutic and embolic agents are currently in use in transarterial therapy for HCC. Doxorubicin is currently the most commonly used

chemotherapeutic agent in single-agent TACE. Triple-agent TACE commonly uses a combination of cisplatin, doxorubicin (Adriamycin), and mitomycin C. For hepatic arterial embolization, spherical embolic materials have generally replaced the older, non-spherical embolic agents because of the availability of more tightly calibrated sizes and greater predictability of flow dynamics. Both temporary (e.g. calibrated Gelfoam and starch microspheres) and permanent (e.g. trisacryl gelatin and spherical polyvinyl alcohol) embolic agents have been used. These range in size from 40 to more than 1000 um in diameter. cTACE is commonly adopted as the first line treatment for patients with large or multinodular HCC and relatively preserved liver function, with no evidence of vascular invasion or extrahepatic spread. cTACE as the standard treatment for intermediate-stage HCC is based on the results of two positive RCTs and a meta-analysis, which demonstrated improved survival outcomes in patients with HCC treated with cTACE compared with the best supportive care.[18–20] In clinical practice, many patients with an early stage of disease (i.e. a single nodule or up to 3 nodules under 3 cm each) with contraindications to curative treatments using liver resection, liver transplantation or local ablative therapy, are commonly treated with cTACE. cTACE also can be used as a bridge therapy before liver transplantation by keeping tumors to be within the size and number required to remain on the waiting list for liver transplantation.

The drug-eluting beads are non-resorbable embolic microspheres that can be loaded with chemotherapeutic agents. They were developed to achieve a more sustained drug release with concomitant embolization. The commercially available drug-eluting beads are composed of various hydrophilic ionic polymers that can bind to anthracycline drugs via an ion exchange mechanism. Up to 37.5 mg of doxorubicin per mL of microspheres can be loaded in 30 min to 2 h. Several microsphere diameters are available, ranging from 40 μm to 900 μm. The safety data with systematic reviews confirmed the similarity in toxicity profile between cTACE and DEB-TACE, with only a slightly lower incidence of severe adverse events after DEB-TACE. Despite the significant differences in the PRECISION V trial on systemic side effects, successive studies reported similar data in the two treatment arms and a negligible amount of systemic complications. In the PRECISION V trial, high doses (nearly doubled to those used in the other studies) of doxorubicin (100–150 mg) were used in cTACE patients and this could be a variable contributing to the high rate of systemic side effects reported.[22] Based on the currently available evidence, there are similar efficacy and safety between the DEB-TACE and cTACE, with only a non-significant trend in favor of DEB-TACE.[21,22]

### Transarterial radioembolization

The tolerance of liver to radiation is relatively low. The tumouricidal dose required is at least 120 Gy. However, doses above 30 Gy for whole liver irradiation may result in radiation hepatitis. The aim of transarterial radiotherapy is to deliver radioisotopes to the liver tumor, where the isotopes reside for a sufficient period to deliver the scheduled dose of radiation. The amount of radiation delivered to the non-tumourous liver parenchyma and other organs should be as low as possible. Based on the rationale of regional therapy, most radioactive substances injected through the hepatic artery are delivered to the tumor, giving a favorable uptake ratio of tumor to normal tissues (T/N). Radioembolization is a transcatheter intra-arterial therapy using the radioisotope Yttrium 90 ($^{90}$Y). It is also called transarterial radioembolization (TARE), selective internal radiation therapy (SIRT), and $^{90}$Y therapy. Microspheres impregnated with $^{90}$Y are delivered through the hepatic artery to the tumors with preferential arterial blood flow. Cumulative radiation dose to the tumor and adjacent tissues are determined by the energies of the radiation, the physical half-life and the biologic fate (biologic half-life of clearance). The therapeutic impact on the tumor can be inferred by the dose rate (dose delivered per unit time). Isotopes with a high energy and short effective half life (incorporating both the physical and biological half-lives) have a high dose rate. The physical half-life and types of

radiation also determine the potential radiation hazards to treatment personnels and to people near to the patient. Isotopes with a long half-life need a long period of radiation protection procedure. This usually applies to isotopes with γ emissions. For isotopes with pure β radiation the requirement for radiation protection is much less as the majority of the radiation can be attenuated by the patient's body. Yttrium-90 ($^{90}$Y) only emits β-rays with a maximum penetration of 11 mm in soft tissues. This means that the abdominal wall is thick enough to shield off all the radiation from the $^{90}$Y microspheres injected into the liver. Only weak secondary X-ray (Bremsstrahlung radiation) can be detected outside the body. Currently, two 90Y products are commercially available: TheraSphere® glass microspheres (BTG, London, United Kingdom) and SIR-Spheres resin microspheres (Sirtex Medical, North Sydney, Australia). Although both microspheres are approved by the US Food and Drug Administration (FDA) for intra-arterial delivery of 90Y, they are different with regard to microsphere composition, size, degree of embolic effect, and specific activity per sphere. There are no randomized studies comparing these two microspheres, but current literature has shown similar clinical outcomes. Many published articles on TARE in HCC have shown similar outcomes in overall survival, which ranged from 15.4 to 17.2 months in intermediate-advanced hepatocellular carcinoma. Meta-analyses showed that TARE is a safe alternative treatment to TACE with comparable complication profile and survival rates.[23–30]

### Conclusion

Loco-regional therapies have emerged as tools for palliation, tumor down-staging, and bridging therapy prior to liver transplantation. Currently, local ablative therapy competes with partial hepatectomy and liver transplantation as the primary treatment for small HCC. Newer techniques such as MWA, and DEB-TACE are being actively evaluated.

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